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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AUDET, MAURY A	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/759,725	PRIESTLEY, E. SCOTT	
	Examiner	Art Unit	
	Maury Audet	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-20* is/are pending in the application.

4a) Of the above claim(s) *18 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/02/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II, in the response of 11/11/2004 is acknowledged. The amendment of the claims to be drawn to compounds all containing the core peptide Asp-Glu-Val-Val-Pro has obviated the original restriction groups. The Examiner is willing to search the non-withdrawn claims 16-17, and 20 as being drawn to the elected peptide species: (H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-phenylpropylboronic acid (+)-pinanediol ester. The traversal is deemed moot. Claims 16-20 are pending. Claims 18 and 20 are withdrawn. Claims 16-17 and 20 are examined on the merits.

Claim Rejections - 35 USC § 112 1st Scope of Enablement

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, although providing support for a "composition" comprising the elected peptide species (or other species): (H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-phenylpropylboronic acid (+)-pinanediol ester, does not reasonably provide enablement for a "pharmaceutical" composition comprising the elected peptide species (or other species): (H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-phenylpropylboronic acid (+)-pinanediol ester. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention.

> The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have

further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for a "pharmaceutical" composition, for the following reasons:

The nature of the invention: The claimed invention is generally drawn to a pharmaceutical composition (claim 19), comprising the elected peptide species (or other species): (H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-phenylpropylboronic acid (+)-pinanediol ester.

The state of the prior art and the predictability or lack thereof in the art:

The art teaches that "NS3 is part of a large polyprotein and associates with other virally encoded protein domains; thus, it is important to characterize these functional sites, which could constitute targets for protein-protein interaction inhibitors. *The NS3 minibody ligands may well be useful molecules for interfering with viral assembly,* as they could inhibit interactions between NS3 and other uncharacterized viral or host factors. *Unfortunately, the lack of a biological assay currently hampers these experiments*" (See Dimasi et al., J Virol. 1997 Oct;71(10):7461-9, specifically "Discussion" page 7468, last ¶; emphasis added).

> The art further teaches that the efficacy of therapeutics is dependent upon factors such as solubility of the drug, bioavailability at the target site, attainment of effective plasma concentrations, solubility in tissues, biotransformation, toxicity, proteolytic degradation, immunological inactivation, rate of excretion or clearance (half-life), deactivation by the liver, hydrolysis in serum, binding to plasma protein, and in the case of antivirals, propensity for emergence of resistant strains (see Benet et al., pp. 3-32, in The Pharmacological Basis of Therapeutics, 8th ed., 1990, page 3, first paragraph; page 5, second column, last partial paragraph, first two sentences; page 10, the paragraph bridging columns 1 and 2; page 18, the paragraph bridging columns 1 and 2; page 20, last full paragraph; and the paragraph bridging pages 20 and 21 and footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO BD> APP>& Inter. 1992).
>
> Isolation, purification, formulation, and delivery of proteins represent significant challenges to pharmaceutical scientists, as proteins possess unique chemical and physical properties. These properties pose difficult stability problems (Abstract). With the recent advances in recombinant DNA technology, the commercial production of proteins for pharmaceutical purposes has become feasible. [] Unfortunately, proteins possess chemical and physical properties which present unique difficulties in the purification, separation, storage, and delivery of these materials. (Manning et al., Pharmaceutical Research, p. 903).

The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification describes in the "Summary of the Invention" that the elected peptide compound may be useful [i.e. in a pharmaceutical composition] as "an inhibitor of hepatitis C virus protease, more specifically, the (hepatitis C virus) NS3 protease". The specification describes that the compounds "are **expected** to inhibit the activity of hepatitis C virus protease" (page 126, emphasis added). Further, the only testing was to the effectiveness of an enzyme assay (page 129, line 30). Additionally, the description of testing the composition/elected compound in a "cell assay" (i.e. referred to above by Dimasi et al. as a "biological assay") is only prophetic, and has not actually been conducted (page 129-130). Although Applicant did *design* a cell assay to overcome this difficulty (HCV will not replicate to lytic infection in cell cultures) (page 129-130); there was no data generated from

actual experiments. Therefore, it is unclear how the composition/elected compound could be administered to a cell either in vitro or in vivo, so as to effectively target/inhibit HCV NS3 protease, or a protease of any other virus. Thus, the specification does not describe that the elected compound was actually found to be useful (i.e. tested) in a "pharmaceutical" composition (i.e. for treating a subject with HCV or any other virus/infection).

The breadth of the claims and the quantity of experimentation needed: The claims are drawn broadly to a "pharmaceutical" composition comprising the elected peptide species (or other species): the elected peptide (H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-phenylpropylboronic acid (+)-pinanediol ester. Absent sufficient teachings in the specification or art sufficient to overcome the teachings of unpredictability in the art as to enablement on whether the elected peptide can be "therapeutically effective" as a "pharmaceutical" composition (for any virus/infection, including HCV); it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 16, it is unclear what the generic (as well as it's respective species) structure of the invention is. Thus, a 'definitive' search of the elected species and broader generic claim could not be carried out. Namely, as to Formula I component "A", it is unclear where the core 5 amino acid peptide attaches to the structure immediately following "A6" and whether Pro or Asp or one of the other peptides attaches to this structure. It is suggested that Applicant amend the genus structure to delete "A" and directly incorporate "Asp-Glu-Val-Val-Pro" and the attached structure thereafter, into the genus structure, so the bonds/structure can be clearly distinguished. Additionally, for clarity of the general structure, it is suggested that the terms "R2" and "R3" simply be deleted from the general structural formula and replaced with "H" in the general structure (as hydrogen is the only contemplated compound for either R2 or R3). Likewise, for clarity, the letter "W" could be deleted form the general structure, and the structure of "W" (the pinanediol boronic ester component) simply incorporated directly into the general structure.

In claim 17, it is unclear what the compound is, because it is unclear what "-4-yl" constitutes between (1,1'-biphenyl) and propylboronic? Appropriate correction is required, or an indication of whether this is the correct structure/name of the compound.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

As noted under § 112 above, a definitive structure of the claimed species/genus could not be ascertained from the claims. However, a number of closely related pieces of prior art have been found, and applied herein, as teaching the core peptide and components of elected compound species (H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-phenylpropylboronic acid (+)-pinanediol ester, absent evidence to the contrary (since it is unclear whether they expressly teach each and every limitation/component/bonding position).

Claims 16-17, and 20, as drawn to the elected peptide species: (H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-phenylpropylboronic acid (+)-pinanediol ester, are rejected under 35 U.S.C. 102(e) as being anticipated by Han et al. (US 6,774,212 B2).

Han et al. teach the core pentapeptide Asp-Glu-Val-Val-Pro (SEQ ID NO: 11) in a composition (abstract) with boronic acid and pinanediol ester (col. 110 examples), and phenylpropyl (see i.e. claim 2).

Claims 16-17, and 20, as drawn to the elected peptide species: (H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-phenylpropylboronic acid (+)-pinanediol ester, are rejected under 35 U.S.C. 102(e) as being anticipated by Zhang et al. (US 6,699,855 B2).

Zhang et al. teach the core pentapeptide Asp-Glu-Val-Val-Pro (SEQ ID NO: 11 col. 79, lines 52-65) in a composition (abstract) with boronic acid and pinanediol ester (i.e. col. 50), and 3-phenylpropyl (i.e. claim 8 compounds).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-17 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Han et al. (US 6,774,212 B2) or Zhang et al. (US 6,699,855 B2).

Han et al. and Zhang et al. are both discussed above.

If not expressly or intrinsically taught therein, obvious various of the compounds containing the elected 5-mer peptide of (H-Asp-Glu-Val-Val-Pro-(1R)-1-amino-3-phenylpropylboronic acid (+)-pinanediol ester in either Han et al. or Zhang et al. would have been obvious to one of ordinary skill in the art at the time of the invention. As Han et al. describes in column col. 110 (prior to teaching the making of variants of the above peptide/compound), "although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various

equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention."

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maury Audet whose telephone number is 571-272-0960. The examiner can normally be reached from 7:00 AM – 5:30 PM, off Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

MA, 12/09/04

CHRISTOPHER R. TATE
PRIMARY EXAMINER